INTRODUCTION

Myopia is a prevalent disease worldwide, and a primary cause of vision impairment in the general population (Flaxman et al., 2017). In some locations in East and Southeast Asia, both myopia and high myopia have a high prevalence (47.0%), which is much higher than that in Central Europe (27.1%), Central Asia (17.0%), and Central Africa (7.0%) (Baird et al., 2020; Pärssinen, 2012; Williams et al., 2015). Moreover, the prevalence of myopia has increased over time, and it has been speculated that the incidence of myopia and high myopia will reach 49.8% and 9.8% of the global population, respectively, by 2050 (Holden et al., 2016). In recent years, there has been a marked increase in the prevalence of myopia at younger ages, indicating that the onset age is increasingly becoming early (Morgan et al., 2018). The earlier the onset of myopia, the more likely that high myopia will develop. High myopia is usually associated with corresponding anatomical abnormalities in the fundus (tessellated retina, macular degeneration, retinal detachment, etc.), further impairing vision (Chang et al., 2013; Wong et al., 2020). Childhood is the critical period for the development of the eyeball. Thus, early clinical interventions (Walline, Lindsley, et al., 2020) that
control myopia progression and inhibit axial elongation, which can cause complications, have important clinical significance.

Emmetropization is regulated by the visual feedback of the retina (Rabin et al., 1981; Rada et al., 1992; Smith 3rd, 1998). Studies on animal models have shown that the blur signal on the retina can regulate eye development (Irving et al., 1992; Smith 3rd et al., 1994). Optical defocus increasing low-order aberrations is a common intervention to induce blur signals on the retina in previous studies (Howlett & McFadden, 2009; Hung et al., 1995; Metlapally & Mcbrien, 2008). However, the image quality on the retina is often affected by both low-order aberrations and high-order aberrations (Charman, 1991, 2005). High-order aberrations can also generate blur signals on the retina. Moreover, it has been shown that there are correlations between many of the high-order aberrations and myopia progression, as indicated by coma and spherical aberration (Philip et al., 2014).

Currently, it is believed that the working principle of myopia control lenses is more likely to be explained by the myopic defocus theory, although induced high-order aberrations can also contribute to the blur signal on the retina (Bao et al., 2021; Lam et al., 2021; Walline et al., 2020). It is still unclear whether the myopia control effect can be expected by solely using high-order aberrations without any defocus component. Clinical results show that these existing interventions have not shown definite and safe myopia control effects, such as the rebound effect and potential side effects of atropine (Jonas et al., 2021) and the individual variation of the optical interventions (Walline, Lindsley, et al., 2020). Therefore, exploring new ideas and methods for myopia control still is significant.

A new patented control lens that can generate blur signals on the retina by solely inducing high-order aberrations has been proposed by a lab from Wenzhou Medical University. The new lens consists of a central optical area of full correction and a control area where many micro-cylinders are arranged in concentric circles. The specific design of the new lens will be described in the section on interventions below. To verify the effectiveness of this lens in controlling myopia progression, we conducted a randomized controlled clinical trial.

This study was part one of a larger research project. The purpose of this article is to: (1) assess whether the study lenses are effective in slowing myopia progression and axial elongation, (2) assess the safety of the study lenses by monitoring the occurrence of adverse events.

2 | MATERIALS AND METHODS

2.1 | Study oversight

We recruited subjects for this study from August 2020 at the Eye Hospital of Wenzhou Medical University. A data and safety monitoring committee (DSMC) oversaw the trial and reviewed the data for patient safety at regular intervals. The study was approved by the ethics committee of the Eye Hospital of Wenzhou Medical University (2020-063-K-55-01) and registered in the Chinese Clinical Trial Registry (registration number, ChiCTR2100053711). This study is in line with the tenets of the Declaration of Helsinki.

2.2 | Study design

This 2-year clinical trial was designed to be a randomized, controlled study with follow-up visits every 6 months and a planned interim analysis after 12 months by the DSMC. Children who may meet the conditions made appointments to participate in screening visits through recruitment advertisements published in social media. The following inclusion criteria for the participants were used: 8–12 years old; cyclopegic SER of −1.00 D to −4.00 D; astigmatism <1.50 D cylinder; anisometropia <1.00 D based on SER; best-corrected visual acuity of +0.1 logMAR or better in each eye, binocular visual acuity of 0.00 logMAR or better; absence of ocular pathology; no history of ocular surgery; no use of myopia control measures in the past 6 months (including progressive multifocal lens, orthokeratology lens, etc.); no systemic diseases such as respiratory and cardiovascular diseases. Eligible subjects enrolled in the study were randomly assigned in a 1:1 ratio to wear cylindrical annular refractive element (CARE) spectacle lenses or single-vision spectacle lenses. Masked examiners performed cyclopegic autorefraction and AL measurements.

2.3 | Interventions

All the lenses used by the test group and the control group were made of polycarbonate. The patented new lenses were prepared for the test group. The lens has a central clear aperture of 9.4 mm in diameter that can provide excellent and stable visual correction, while its peripheral side-vision zone is covered by the annular micro-cylinder array. The annular micro-cylinders are concentrically patterned with a constant radial interval of 1.2 mm (Figure 1). Along the radial direction, the filling factor of the micro-cylinder is 60% in each period. The unoccupied areas between adjacent micro-cylinders share the common base power of the central clear aperture. The micro-cylinder brings an addition of +8.00 D cylinder power to the base power of the occupied areas.

When the plane wave incidences on the peripheral side-vision zone of the lens, the emergent wavefront at the back vertex sphere, compared to that of the single-vision spectacle lenses (SVL), features the regularly distributed perturbation due to the additional phase retardance caused by the micro-cylinder array. Because of the discontinuity of the lens surface with the micro-cylinder array, such a wavefront perturbation can be interpreted as extreme high-order wavefront aberrations that cannot be fully expressed by the standard Zernike polynomials, and will eventually lead to a blurred image for the peripheral field of view.

2.4 | Outcome variables

The primary outcomes were the 1-year change in spherical equivalent cyclopegic autorefraction and axial...
length. Three measures of central refractive error were conducted on each eye with NIDEK ARK-510A and averaged. Cycloplegia was achieved using 2 drops of 1% cyclopentolate separated by 5 min. Measurements were taken 30 min after the second drop of cyclopentolate. The 1-year change from baseline in axial length was measured using IOL Master700 (Carl Zeiss Meditec AG, Jena, Germany) and an average of five measurements was taken.

Secondary outcomes presented in this article include visual acuity, adverse events, and adherence. Other secondary outcomes not addressed in this article include choroidal thickness and choroidal vascularity (blood vessels in the back of the eye that may signal changes in myopia); and report of myopia risk factors, binocular vision and accommodation symptoms, and vision-specific quality of life. Visual acuity was measured using a multifunctional VA tester (NIDEK RT-5100; Eye Vision Development Co, Wenzhou, China) under 80 cd/m² at a viewing distance of 5.5 m. Adherence was monitored by parental reports of the participant’s daily wearing hours. Furthermore, the participant’s daily outdoor activity time was also reported as it might affect myopia progression. Adverse events were reported based on phone interviews 1 week after dispensing and every 6-month through self-administered questionnaires. Serious adverse events were defined as “fatal, life-threatening, or resulted in a two-line loss of best corrected visual acuity or hospitalization.” Severe adverse events were defined as “incapacitating or sight-threatening.” Moderate adverse events “interfered with daily activities and/or were treated with prescription medication.”

2.5 | Sample size

The minimum sample size was 72, based on projections of a 33% reduction in the amount of SER and AL progression for treatment groups compared with the control group and a mean SER progression of 1.50 D with an SD of 0.75 D and converted AL progression of 0.6 mm with an SD of 0.02 mm after 2 years in the control group based on previous findings (Bao et al., 2021). This was based on a two-sided statistical test with a 5% type I error threshold, 90% power, and a 10% drop-out rate (Hasebe et al., 2014; Yang et al., 2009).

2.6 | Statistical analysis

We included all data from patients who completed each visit during the 1-year follow-up period for analysis. The mean values for ocular parameters measured in the right eye were used, as no significant differences in SER changes (mean difference of 0.023 D, \( p = 0.38 \); correlation between eyes, \( r = 0.896, p < 0.001 \)) and AL changes (mean difference of 0.01 mm, \( p = 0.60 \); correlation between eyes, \( r = 0.743, p < 0.001 \)) were observed between the eyes.

The statistical analyses were performed using SPSS Statistics 24.0 (IBM, Armonk, NY, USA). The normality of the data was evaluated using the Shapiro–Wilk test. \( \chi^2 \) test and independent-sample \( t \)-test were used to assess intergroup differences in the categorical and continuous variables, respectively. Our analysis was performed using complete case data without imputation for missing data and dropouts. We performed analyses using a linear mixed model after adjusting for baseline age, gender, SER, AL, and age of myopia onset. When analysing 1-year changes in ocular parameters and mean value at each visit, \( p \)-values of <0.05 were considered statistically significant. When analysing 6-month changes in ocular parameters, \( p \)-values of <0.025 were considered statistically significant to avoid increasing the probability of type I errors.

3 | RESULTS

3.1 | Study population

Of the 118 enrolled participants, 96 (81.4%) were included in the analyses (Figure 2). Ten participants did not attend the 6-month visit and 12 did not attend the 1-year visit. Approximately 50% of the participants were female, and the mean (SE) age was 10.4 (0.6) years at baseline. The mean (SE) right eye cycloplegic spherical equivalent was −2.67 (0.66) D, and the mean (SE) right eye axial length was 24.75 (0.77) mm at baseline. The demographic and ocular characteristics of each treatment group at baseline are shown in Table 1.

**FIGURE 1** The physical picture of the patented lens (the left). Within the specific aperture range of the lens, the annular micro-cylinder array is centered on the geometric center of the lens (1-the occupied area with annular micro-cylinders, and 2-the spacing of two adjacent micro-cylinders) (the right).
Table 2 shows the mean (±SE) changes in myopic refractive error (1 year) for 96 subjects randomized to one of two groups in the study. The 1-year progression of myopia in the CARE group (−0.56 ± 0.46 D) was smaller than that in the SVL (−0.71 ± 0.39 D) group, with a −0.15 D difference in the two groups and a 21.1% reduction in the progression of myopia in the CARE group compared to that in the SVL group. The mean differences of the first 6-months and second 6-months progression of myopia between the CARE group and the SVL group were −0.09
D and −0.05 D, respectively; neither of them was statistically different (19.1%, \( p = 0.22 \) and 20.8%, \( p = 0.36 \)).

In linear mixed model analysis, sex, age of myopia onset, baseline age, and baseline SER were not significantly associated with changes in SER (\( p > 0.05 \)). The model-adjusted 1-year changes in SER were \(-0.56 \pm 0.06 \) D for the CARE group and \(-0.71 \pm 0.07 \) D for the SVL group (Figure 3a; \( F = 2.546, p = 0.11 \)). The model-adjusted 6-month changes in SER were also similar in the two groups (the first 6 months: \( p = 0.19 \); the second 6 months: \( p = 0.46 \)).

### 3.3 | Changes in AL

Table 2 shows the unadjusted mean (±SE) increases in AL for 96 subjects who were randomized into either one of the two groups in the study. A significant difference was observed between the CARE group and the SVL group in the 1-year elongation of AL (\( t = -2.661, p = 0.009 \)). Compared to SVL, CARE had a reduced AL elongation by 0.10 mm, with a 27.8% reduction. The mean differences in the first 6 months and the second 6 months’ elongation of AL between the two groups were 0.04 mm (17.4%, \( p = 0.18 \)) and 0.06 mm (46.2%, \( p = 0.001 \)), respectively.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Unadjusted mean changes in SER and AL in each group.</th>
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<tbody>
<tr>
<td></td>
<td>CARE (n = 52)</td>
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<tr>
<td>Cycloplegic SER, D</td>
<td></td>
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<tr>
<td>Baseline to 6-months</td>
<td>(-0.38 \pm 0.35 )</td>
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<tr>
<td>6-months to 12-months</td>
<td>(-0.19 \pm 0.26 )</td>
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<tr>
<td>Baseline to 12-months</td>
<td>(-0.56 \pm 0.46 )</td>
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<tr>
<td>Axial length, mm</td>
<td></td>
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<tr>
<td>Baseline to 6-months</td>
<td>0.19 ± 0.12</td>
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<tr>
<td>6-months to 12-months</td>
<td>0.07 ± 0.07</td>
</tr>
<tr>
<td>Baseline to 12-months</td>
<td>0.26 ± 0.18</td>
</tr>
</tbody>
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Note: Data are presented as mean ± SEs. *\( p < 0.05 \) and **\( p < 0.025 \) indicate significant differences between the two groups.

Abbreviations: AL, axial length; CARE, Cylindrical Annular Refractive Element spectacle lenses; D, diopters; SER, spherical equivalent refraction; SVL, single-vision spectacle lenses.

The linear mixed model analysis showed that the baseline age and the baseline AL were significantly associated with changes in AL (\( p = 0.009 \) and \( p = 0.002 \), respectively). The model-adjusted 1-year changes in AL were \(0.27 \pm 0.02 \) mm and \(0.35 \pm 0.02 \) mm for the CARE and SVL groups, respectively (Figure 3b); there was a significant difference between the two groups (\( F = 6.692, p = 0.011 \)). Moreover, the model-adjusted first 6-months changes in AL were similar between groups (\( F = 1.725, p = 0.19 \)), but significant differences were found in the second 6-months changes in AL between the CARE and SVL groups (\( F = 11.225, p = 0.001 \)).

### 3.4 | Secondary outcomes

At the final visit, the mean high-contrast distance log-MAR visual acuity (SE) was −0.09 (0.02) for the CARE group and −0.09 (0.03) for the single-vision group (\( p = 0.84 \)). The distribution of daily wearing hours (\( p = 0.43 \)) and outdoor activity hours (\( p = 0.43 \)) in the two groups were not significantly different (Table S1). In the CARE group, the change in SER from 6 months to 12 months of the longer wearing times did show an obvious difference compared to the shorter wearing times (\( p = 0.018 \)) group (Figure S1).

The two groups had no complaints or discomfort based on the 1-week phone interview and every 6 months questionnaires. Adverse events (untoward medical occurrence, unintended disease or injury, or any untoward clinical signs related to the interventions) were not reported.

### 4 | DISCUSSION

Based on current research data, wearing CARE lenses slowed myopia progression by 0.14 D and eye growth by 0.09 mm compared with wearing single-vision spectacle lenses.

In this study, there was a significant difference in axial elongation between the CARE group and the SVL group. Previous studies have shown that most types of myopia control lenses are generally more effective in slowing
myopia progression in the early stages of wearing (Bao et al., 2021; Charman & Radhakrishnan, 2021; Lam et al., 2020). In our study, the absolute and relative change in axial length of the CARE group suggested a better effect of slowing myopia progression in the latter half of the year. We speculate that it may be related to the increased adherence of the participants. A study of multifocal soft contact lenses showed that the effect of myopia control was positively correlated with lens-wearing time (Lam et al., 2014). At each visit, the researcher emphasized the importance of wearing glasses consistently to the participants, and the reduction in myopia progression in turn led to participants' improved adherence. We also found that subjects with longer wearing times in the CARE group had less myopia progression in the second 6 months.

In our study, the change in SER did not show an obvious difference between the two groups. There are three obvious possible reasons for this. First, there was still some residual regulation after cycloplegia; the amount of residual accommodation varied among individuals, affecting the final measurement of refractive error (Ebri et al., 2007; Khurana et al., 1988). Second, the repeatability precision of autorefraction after cycloplegia was not high enough, so it was difficult to accurately estimate the mean value of spherical equivalent refraction (Wilson et al., 2020). Although the repeatability of autorefraction after cycloplegia is much higher than that without cycloplegia, we thought that axial length might be a more sensitive and reliable outcome (Brennan et al., 2021). Third, the reduction in myopia progression of the CARE group was too slight to show a significant difference between the two groups. However, we found that the difference increased over time. The difference in myopia progression may become obvious at the 18-month or 24-month visit. However, there could be many other reasons, such as measurement errors between different researchers, and so on.

The results of our study show that CARE lenses designed to induce higher order aberrations can indeed slow axial elongation compared with single-vision spectacle lenses. This seems to prove the intervention of higher order aberrations in myopia progression in turn. Previous studies on other interventions for myopia control have also found changes in higher order aberrations. Progressive multifocal lenses showed different distributions of higher order aberrations in different regions (Ghosh et al., 2011). Compared to the single-vision soft contact lens, the soft contact lens for myopia control has a different component of higher order aberrations (Hughes et al., 2020). After cycloplegia, significant changes in various types of higher order aberration were also observed (Hiraoka et al., 2013). Given all this, the existing interventions for myopia control may be explained by the theory of higher order aberrations.

The current study reports the first-year interim results of a 2-year clinical trial in Chinese children. The reduction in axial elongation might not be enough to affect the endpoint of myopia progression. The ultimate myopia control effect requires further confirmation with the results obtained from the whole duration of the clinical trial. In this study, we learned the daily wearing times and daily outdoor times of all participants by a questionnaire at every visit. Although this method is not objective enough, assessing the compliance of the subjects by questionnaire is already a relatively accurate and common method in previous studies (Bao et al., 2021, 2022). Moreover, we did not take into account the effect of near-work hours on myopia progression (Huang et al., 2015; Wen et al., 2020). In future research, we hope to find a portable device that can continuously monitor the time of wearing glasses, outdoor activities, and near-work to solve the above limitations. The generalizability of the results regarding the myopia control effect of CARE lenses may be limited to Chinese children. Thus, future trials in other ethnic populations are needed.

In summary, cylindrical annular refractive element spectacle lenses significantly reduced axial elongation in children. No treatment-related adverse events were reported, reflecting the comfort and safety of CARE for myopia control in children. Thus, the use of CARE instead of conventional SVL for myopia correction would be a better strategic approach to reduce myopia progression. Since the effect of slowing axial elongation of CARE in the second 6 months is better than that in the first 6 months, we look forward to the results of the 2-year study. Moreover, we have further optimized the design of the patented lens for the following phase two study, and the myopia control effect of the new lens will be reported later.

**AUTHOR CONTRIBUTIONS**

XM, JQ, and YL: study concept and design. XL, PW, MS, MC, JW, JH, and ZC: data collection and management. XL and PW: analysis and interpretation of data. XL and PW: writing the manuscript. XM, JQ, and YL: critical revision of the manuscript. All authors read and approved the final manuscript.

**ACKNOWLEDGEMENTS**

The authors wish to thank Risheng Xia and Jisheng Xia from Gino Optics for their technical support in lens manufacture for this study.

**FUNDING INFORMATION**

This study was supported by the National Natural Science Foundation of China (82101176), Key Research and Development Plan in Zhejiang Province (2021C03102), and Health Technology Plan Project in Zhejiang Province (2021KY808).

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**REFERENCES**


**SUPPORTING INFORMATION**

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